Anastrozole in Localized Breast Cancer

**Speaker:** David Cella, PhD, Director of Center on Outcomes, Research and Education (CORE), Evanston Northwestern Healthcare, and Professor, Northwestern University Medical School, Evanston, Illinois.

A five-year quality-of-life (QOL) follow-up study of adjuvant endocrine therapy for postmenopausal women with early breast cancer in the Arimidex or Tamoxifen Alone or in Combination (ATAC) trial demonstrated the superiority of anastrozole (Arimidex®; AstraZeneca) over tamoxifen (Nolvadex®, AstraZeneca) without a detrimental impact on overall QOL. Findings were reported in the ATAC Completed Treatment Analysis (CTA).

ATAC, a double-blind, randomized study, was designed to compare five years of primary adjuvant treatment with anastrozole alone, tamoxifen alone, or the combination of the two in 9,366 postmenopausal women with localized breast cancer. At a median follow-up of 68 months, the CTA showed that anastrozole, compared with tamoxifen, was superior in efficacy and tolerability, offering prolonged disease-free survival, time to recurrence and to distant recurrence, and a significant reduction in contralateral breast cancers.

In a subprotocol of the ATAC trial, the impact of adjuvant anastrozole or tamoxifen treatment after five years was investigated. Formal analyses compared 335 patients in the anastrozole group and 347 in the tamoxifen group. The Functional Assessment of Cancer Therapy–Breast (FACT-B) Questionnaire (Version 3) and an additional Endocrine Symptom Subscale Questionnaire were used to assess QOL. The primary endpoint was the Total Outcomes Index, a summation of physical components of QOL.

The QOL assessments were made at baseline, at three months, at six months, and every six months thereafter, up to and including confirmation of disease recurrence, cessation of the study therapy, or withdrawal from the subprotocol.

There were no statistical differences in mean Total Outcomes Index scores between the tamoxifen and anastrozole patients, as confirmed by a longitudinal analysis. The mean Index scores showed continual slight improvements in both groups of patients. Sixty-seven percent of patients in both treatment groups experienced clinically meaningful improvement from baseline in their Index scores at any point in their follow-up, and 17% of patients in both groups did so during each assessment.

Differences in individual endocrine symptoms, as identified from the responses in the patient questionnaires, were generally consistent with the known side effects of tamoxifen and anastrozole. These differences in adverse effects included increased vaginal discharge and bleeding in the women taking tamoxifen and increased vaginal dryness and dyspareunia in those taking anastrozole.

Trastuzumab and HER2-Positive Metastatic Breast Cancer

**Speaker:** Michele Marty, MD, Professor and Head of Therapeutic Innovation, Onco Haematology, Saint Louis University Hospital, Paris, France.

New 24-month data indicate long-term survival benefits following the addition of trastuzumab (Herceptin®, Genentech/Roche) to docetaxel (Taxotere®, Sanofi-Aventis) chemotherapy, when compared with docetaxel alone, in patients with HER2-positive metastatic breast cancer. The number of patients who were still living three years after starting trastuzumab therapy was twice that of patients in the docetaxel-only studies.
A total of 188 HER2-positive patients were randomly selected to receive docetaxel 100 mg/m² every three weeks for six cycles and trastuzumab 4 mg/kg as a loading dose, followed by 2 mg/kg weekly, versus docetaxel given alone every three weeks for six cycles until disease progression. Patients whose disease progressed while they were receiving docetaxel alone could then cross over to receive trastuzumab.

Over the long term, twice as many women who received the combination therapy (33%) were alive more than three years after the inception of treatment, compared with women who received only docetaxel (16%). Of the 15 patients who survived more than three years in the docetaxel-only group, most had crossed over to trastuzumab, for a total of 91% of all long-term patients receiving this drug.

These findings strongly support the first-line use of trastuzumab plus taxanes in these patients. The data confirm that establishing the patient’s HER2 status is an essential step in disease management.

**Zolendronic Acid and Bone Mass in Women with Breast Cancer**

**Speaker:** Adam Brufsky, MD, PhD, Co-Director, Magee Women’s Hospital/University of Pittsburgh Cancer Institute, Comprehensive Breast Cancer Center, and Assistant Professor of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania.

“Up-front” zolendronic acid (Zometa®, Novartis), an intravenous (IV) bisphosphonate, when given with adjuvant letrozole (Femara®, Novartis) therapy, was able to inhibit bone loss in postmenopausal women with early breast cancer. At 12 months, bone mineral density (BMD) was significantly increased in patients receiving this regimen, compared with patients who received the aromatase inhibitor letrozole and delayed zolendronic acid.

The multicenter Zometa–Femara Adjuvant Synergy Trial (Z-FAST), an open-label, randomized study, enrolled 602 postmenopausal women with stage 1, 2, or 3 estrogen receptor–positive (ER+) and/or progesterone receptor–positive (PR+) breast cancer. The women had undergone complete tumor resection and had no clinical or radiological evidence of recurrent or metastatic disease.

They started taking letrozole 2.5 mg/day and were randomly assigned to either (1) take zolendronic acid 4 mg as a 15-minute IV infusion every month beginning on the first day or (2) wait before starting a 4-mg, 15-minute IV infusion of zolendronic acid every six months if the post-baseline BMD T-score was below –2.0 standard deviations or after the occurrence of a bone complication.

The patients receiving zolendronic acid up front showed a mean increase of 1.9% in lumbar spine BMD; the patients who received zolendronic acid on a delayed schedule showed a decrease of 2.4% in BMD, for a 4% relative difference. Total hip BMD was also significantly higher with up-front bisphosphonate therapy than with delayed treatment. Most important, 8% of patients receiving the delayed therapy exhibited decreases in BMD at the 12-month follow-up evaluation and required the initiation of zolendronic acid therapy.

Patients currently in the study are to be treated for a maximum of five years or until disease progression. A total of 342 of the 602 patients (170 up front/173 delayed) are evaluable for 12 months of lumbar spine BMD.

**Gemcitabine-Containing Regimens in Early-Stage Non–Small Cell Lung Cancer**

**Speaker:** Frank C. Detterbeck, MD, Professor, Division of Cardiothoracic Surgery, Department of Surgery, University of North Carolina Medical School and Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina.

Neoadjuvant chemotherapy with gemcitabine (Gemzar®, Eli Lilly), as part of either platinum or non-platinum doublets (dual therapies), was found to be feasible and well tolerated. This regimen offered rates of resectability, response, and survival that were competitive with other reports of this treatment strategy when given prospectively to patients with early-stage non–small cell lung cancer (NSCLC).

Eighty-seven patients with clinical stage 1 (n = 61) and stage 2 (n = 26) NSCLC were enrolled in the GINEST Project. This study consisted of two similar, randomized phase 2 trials that tested platinum and non-platinum regimens, including gemcitabine, in patients with early-stage NSCLC.

In trial 1, 59 patients were selected to receive prospective chemotherapy with either gemcitabine 1,000 mg/m² on days 1 and 18 and carboplatin (Paraplatin®, Bristol-Myers Squibb) with an area-under-the-curve (AUC) concentration of 5.5 on the first day or gemcitabine plus paclitaxel (Taxol®, Bristol-Myers Squibb) 200 mg/m² on the first day.

In trial 2, 28 patients were assigned to take gemcitabine plus carboplatin, on the same basis, or gemcitabine plus cisplatin (Platinol®, Bristol-Myers Squibb) 80 mg/m² on the first day. All of the doublets were given every 21 days for three cycles.

As of this writing, the overall rate of complete resection was 73% for 83 patients; 5% of the patients underwent an incomplete resection, and 18% of patients did not undergo surgery for various reasons. The perioperative mortality rate was 2%. One pathological complete response (CR) has been validated with gemcitabine/paclitaxel, and one CR has been validated with gemcitabine/cisplatin.

In the three different doublet regimens, there were 20 partial responses and 38 patients who had stable disease. Seven patients had progressive disease, and the rest of the patients were lost to follow-up.

The most common toxicities overall were grade 3 and 4 leukopenia (in 24 patients) and thrombocytopenia (in seven patients). Even though grade 3 and 4 nonhematological toxicities were uncommon, arthralgia developed in 93 patients; neurotoxicity, in three patients; diarrhea, in two patients; cellulitis, in two patients; and asthenia, in one patient. The survival rate at one year was 84.9%.

**Oblimersen Sodium for Advanced Malignant Melanoma**

**Speaker:** John Kirkwood, Professor of Medicine and Director, the Melanoma Program, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania.
Long-term follow-up results for a minimum of 24 months demonstrated that adding oblimersen sodium (Genasense®, Genta), also called Bcl-2 antisense, to dacarbazine (DTIC-Dome®, Bayer)—the only chemotherapy agent approved for the treatment of advanced melanoma—achieved a significant increase in “durable” responses (lasting longer than six months) and a near-significant trend toward increased survival, when compared with dacarbazine alone in patients with this cancer.

A total of 771 patients with stage 4 melanoma or stage 3 disease that was not surgically resectable were randomly selected to receive oblimersen on an outpatient basis at 7 mg/kg per day by continuous IV infusion for five days, followed by dacarbazine 1,000 mg/m². Patients in the chemotherapy-alone arm received the same dose of dacarbazine without oblimersen.

The primary endpoint of the trial was overall survival. Secondary endpoints included progression-free survival, tumor response, and durable response.

After a minimum of 21 months of follow-up, the estimated 24-month overall survival was nine months for the oblimersen/dacarbazine patients, compared with 7.8 months for the dacarbazine-alone patients. This difference represented a strong trend that approached, but did not reach, statistical significance. Patients treated with oblimersen and dacarbazine, however, showed a significant increase in median progression-free survival to 2.4 months, compared with 1.6 months for patients receiving dacarbazine alone.

The overall response rates were 12.4% (11 CRs) with oblimersen/dacarbazine and 6.8% (two CRs) with dacarbazine alone. In the combination treatment group, seven of the 11 patients with CRs were living and disease-free at more than 38, 36, 27, 27, 27, and 26 months, respectively. In the dacarbazine arm, one CR patient was alive and disease-free at more than 27 months. The second patient died as a result of progressive disease at 20 months.

With the oblimersen/dacarbazine treatment, 28 patients (7%) achieved a durable response rate, and with dacarbazine alone, 13 patients (3%) achieved this rate. This 115% improvement rate thus favored the addition of oblimersen to dacarbazine.

**Bevacizumab in Recurrent Ovarian Cancer**

**Speaker:** Agustin Garcia, MD, Director of Breast Cancer Research, Women’s Cancer Research Institute, Samuel Oschin Comprehensive Cancer Institute, Cedars–Sinai Medical Center, Los Angeles, California.

Bevacizumab (Avastin™, Genentech), an anti-angiogenesis monoclonal antibody that targets and blocks the function of vascular endothelial growth factor, was able to shrink ovarian tumors and slow the progression of the disease in women with recurrent ovarian cancer when it was combined with low-dose chemotherapy containing oral cyclophosphamide (e.g., Cytoxan®, Bristol-Myers Squibb).

Twenty-nine patients were enrolled in a phase 2 clinical trial to evaluate the activity and toxicity profile of the combination of bevacizumab and low-dose, timed (metronomic) oral cyclophosphamide and to explore serological markers of angio-

**Standard Therapy plus Oxaliplatin for the Treatment of Colorectal Cancer**

**Speaker:** Norman Wolmark, MD, Chairman and Professor, Department of Human Oncology, Drexel University College of Medicine and Allegheny Cancer Center, and Chairman of the National Surgical Adjuvant Breast and Bowel Project.

The addition of oxaliplatin (Eloxatin®, Sanofi-Aventis) to standard fluorouracil (5-FU) (Efudex®, Roche)/leucovorin (LV) (Wellcovorin®, Immunex) therapy (FULV) significantly improved three-year disease-free survival in patients with early-stage colorectal cancer, markedly reducing the risk of disease recurrence by 21%.

In a phase 3 trial, 2,407 patients with stage 2 (28.6%) or stage 3 carcinoma of the colon were randomly assigned to receive either FULV, with an 5-FU 500-mg/m² IV bolus weekly for six weeks plus LV 500 mg/m² IV weekly for six weeks, each eight-week cycle for three cycles, or the same FULV regimen with oxaliplatin 85 mg/m² IV (FLOX) administered at weeks 1, 3, and 5 of each eight-week cycle for three cycles.

The primary endpoint was disease-free survival. Events were defined as a first recurrence, a second primary cancer, or death.

At a median follow-up of 34 months, 272 events were noted with FLOX therapy, resulting in a disease-free survival rate of 76.5%. This compared with 332 events with FULV, with a disease-free survival rate of 71.6%. Fourteen patients died while taking FULV, and 15 patients died while taking FLOX.

Adverse effects were similar in both treatment groups, although more oxaliplatin patients (8%) experienced neurosensory toxicity than the FULV patients (1%). Diarrhea and dehydration requiring hospitalization were more common with oxaliplatin (4.7% of patients) than with FULV (2.8% of patients).

**Lenalidomide Therapy for Patients with Myelodyplastic Syndromes**

**Speaker:** Alan F. List, MD, Professor of Oncology and Medicine, and Program Leader, Hematologic Malignancies, Department of Interdisciplinary Oncology, H. Lee Moffitt Cancer Center, University of South Florida, Tampa Bay, Florida.

Lenalidomide (RevLimid®, Celgene), an anti-angiogenic agent that is similar to thalidomide, appeared to prevent the

*continued on page 413*
need for blood transfusions in patients with transfusion-dependent myelodysplastic syndromes (MDSs) and a chromosome 5q31 abnormality. The regimen even reduced or eliminated the genetic abnormality that characterizes the disease in this subset of patients.

In a multicenter phase 2 study, 146 patients with confirmed disease were given oral lenalidomide 10 mg once daily. The deletion of a region of genetic material on the long “q” arm of chromosome 5 was present in all of the patients.

After 24 weeks, 93 patients (63% of the treated population) responded positively to lenalidomide and no longer needed transfusions. A cytogenetic (CTG) response was achieved in 76% of the transfusion-independent patients, with 55% of them having complete CTG responses.

After a median follow-up of 9.3 months, 91% of the responding patients continued to respond to lenalidomide, with a failure rate of only 9% in the responders. The most common adverse effects—neutropenia in 39% of the patients and thrombocytopenia in 35% of the patients—necessitated the interruption of treatment or a reduction of the lenalidomide dose.

This trial was initiated in July 2003, and all patients who responded to the drug will continue to take it for as long as it remains effective.

### Raloxifene for Protection Against Endometrial Cancer

**Speaker:** Angela DeMichele, MD, Assistant Professor of Medicine, Abramson Cancer Center and the Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, Pennsylvania.

A study of raloxifene (Evista®, Eli Lilly), a selective estrogen modulator, along with tamoxifen (Nolvadex®, AstraZeneca) demonstrated the former agent’s protective effect on the endometrium, significantly lowering the risk of endometrial cancer.

In this case–control study, the use of raloxifene and tamoxifen was compared in 547 women with endometrial cancer and in 1,412 women without cancer. The women with cancer were part of the Women’s Insights and Shared Experiences (WISE) study, a project of the University of Pennsylvania’s School of Medicine investigation of hormone-related cancers in women.

Patients in the control group were recruited by random-digit telephone dialing in Philadelphia. Previous findings had indicated that tamoxifen sometimes increased the risk of endometrial cancer; unlike tamoxifen, raloxifene does not stimulate estrogen receptors in the uterine lining.

Among the study patients, 18 women (3.3%) had used raloxifene in the past and 34 (6.2%) had used tamoxifen. In the control group, 93 women (6.6%) had used raloxifene and 34 (2.2%) had used tamoxifen. The risk of endometrial cancer in the women taking tamoxifen was 50% higher than in the non-users, whereas raloxifene users experienced a 50% reduction in risk.

The benefit of raloxifene, in terms of endometrial cancer risk, remained constant, even among the women who took the drug for less than three years.